

# New Insights on Childhood Lupus Nephritis

Rodrigo Marchi-Silva<sup>1,2</sup>, Bruna Martins De Aquino<sup>1,2</sup>, Ana Carolina Londe<sup>1,2</sup>, Taís Nitsch Mazzola<sup>3</sup>, Paulo Rogério Julio<sup>4</sup>, Theresa Wampler Muskardin<sup>5,6</sup>, Simone Appenzeller<sup>2,7</sup>

<sup>1</sup>Medical Pathophysiology Graduate Program, School of Medical Science, Universidade Estadual de Campinas, Campinas, Brazil; <sup>2</sup>Autoimmunity Lab, School of Medical Science, Universidade Estadual de Campinas, Campinas, Brazil; <sup>3</sup>Center for Molecular Biology and Genetic Engineering (CBMEG), Universidade Estadual de Campinas, Campinas, Brazil; <sup>4</sup>Child and Adolescent Graduate Program, School of Medical Science, Universidade Estadual de Campinas, Campinas, Brazil; <sup>5</sup>Hospital of Special Surgery, Department of Medicine, New York, NY, USA; <sup>6</sup>Weill Cornell Medicine, Department of Medicine and Department of Pediatrics, New York, NY, USA; <sup>7</sup>Department of Orthopedics, Rheumatology and Traumatology, School of Medical Science, Universidade Estadual de Campinas, Campinas, Brazil

Correspondence: Simone Appenzeller, Faculdade de Ciências Médicas (FCM)/Hospital de Clínicas (HC) – UNICAMP, Vital Brasil Street, 251, Campinas, SP, 13083-888, Brazil, Tel +55 11 98887-8693, Email [appenzel@unicamp.br](mailto:appenzel@unicamp.br)

**Abstract:** Approximately one in five patients with systemic lupus erythematosus (SLE) has disease-onset during childhood (cSLE). Lupus nephritis is more common in cSLE than adult-onset SLE and is associated with significant and increased morbidity and mortality. In this article, we review lupus nephritis in cSLE, including pathogenesis, diagnosis, biomarkers, and management through PUBMED search between July and December 2024. Diagnosis of lupus nephritis is made in 93% of cSLE patients during the first 2 years of disease. The majority of patients have active disease in other organs, and nephrotic range proteinuria and hypertension is frequently observed at diagnosis. Class III and IV are observed in over 50% of renal biopsies and progression to end-stage renal disease varies across cohorts. Major progress made in recent years includes adjustment of the proportion of fibrous crescents when scoring nephritis in cSLE to better discriminate kidney disease outcomes, and development of non-invasive biomarkers to identify renal disease activity and damage. It is anticipated that accurate non-invasive biomarkers will foster multicenter studies and help identify new treatment approaches to improve outcomes in cSLE nephritis.

**Keywords:** lupus nephritis, childhood-onset SLE, treatment

## Introduction

Systemic lupus erythematosus (SLE) is a chronic multisystem disease, characterized by complement activation, immune complex deposition, and organ damage.<sup>1,2</sup> Childhood-onset SLE (cSLE) is defined as SLE with disease-onset prior to the age of 18 and comprises approximately twenty percent of all SLE patients.<sup>3,4</sup> SLE patients who have had childhood onset of disease have different frequencies of organ involvement than patients with adult-onset SLE (aSLE), and typically experience more severe disease.<sup>5,6</sup> In meta-analysis, ten to thirty percent higher prevalence of kidney involvement was observed in cSLE when compared to aSLE.<sup>7</sup> The differences in reported rates are due to discrepancies in biopsy policies, cohort size, and racial cohort composition.<sup>8</sup> Nephritis is among one of the most frequent manifestations in cSLE, occurring in thirty-two to eighty-two percent, depending on the patient's race and ethnicity and the study methodology.<sup>9–15</sup> Comparing the frequency of nephritis in cSLE to aSLE, cSLE has an OR of 1.62 (95% CI 1.21–2.16).<sup>7</sup> Nephritis in cSLE is associated with increased morbidity and mortality.<sup>14,16</sup> Over recent decades, earlier diagnosis and treatment has improved outcome. Yet, up to one in four children with cSLE may develop end-stage renal disease during the course of SLE.<sup>17,18</sup> In most cases of cSLE, nephritis occurs in the first two years of disease-onset, which highlights the need for close follow-up with adequate screening.<sup>19</sup> The differences in clinical presentation and outcome of nephritis in cSLE and aSLE are summarized in Table 1. This review summarizes current knowledge regarding pathogenesis, diagnosis, biomarkers, and management of nephritis in cSLE.

**Table 1** Comparison Between Nephritis Adult and Pediatric cSLE. Adapted from<sup>7,8,20–37</sup>

	cSLE	aSLE
<b>Frequency of LN</b>		
Overt LN	32–82%	20–40%
Silent LN	31–55%	15–75%
Renal vascular lesions	22%	53–75%
<b>Demographic data</b>		
Sex	73% female	84% female
Age (mean)	12 years	35 years
Nephritis in relation to disease duration	Nephritis 93% in the first 2 years of disease	
<b>Clinical presentation</b>		
Nephrotic range proteinuria	~56.7%	~16%
Hypertension	~45.7%	~58%
Acute kidney injury	19%–51%	~10%
Systemic disease	cSLE>aSLE	
<b>Risk factors</b>		
	Low C3 or C4 Younger age	Younger age Male Hispanic
Complete Remission	50–80%	~60%
Partial remission	~30%	~33%
Renal Flares	25%–60%	30–40%
Progression to CKD	1–20%	4.3–6.7%
Risk factors	Non-Caucasian> Caucasian Flares Non-adherence ≥10% fibrous crescents Proliferative components Hypertension	Interstitial fibrosis Flares Male sex Obesity Hypertension

## Materials and Methods

### Search Strategy

References included in this narrative review were obtained from PUBMED searches conducted between July and December 2024.

### Pathogenesis

Pathogenesis of lupus nephritis involves a complex interaction of genetic risk factors, interferon activation, cytokines and complement activation in addition to infiltration of B and T cells in the kidney.<sup>38</sup> Innate immunity and type I interferon (IFN-I), which bridges innate and adaptive immunity, have important roles in the pathogenesis of SLE.<sup>39,40</sup> The presence of a high IFN-I signature in circulation is associated with an earlier development of nephritis. In kidney biopsies, IFN-I signaling is associated with greater disease activity, as well as an increased frequency of class III and IV among different lupus nephritides.<sup>41–43</sup>

Cohort studies have identified and validated gene polymorphisms that confer susceptibility to lupus nephritis. Several different pathways have been implicated by the genes affected, including lymphocyte activation and signaling (eg, *BANK1*, *PTPN22*, *TNFSF4*, and *HLA-DR*), inflammation (eg, *TNFAIP3*, *IRAK1* and *ITGAM*), IFN-I production (eg, *IRF5*, *IRF7*, *TLR7*, *TLR8*, *TLR9* and *STAT4*), DNA clearance (eg *DNASE1*, *DNASE1L3* and *TREX1*) and the complement pathway (eg, *CIQ* and *C4*).<sup>38,44</sup> Single-cohort studies have documented and validated several genes that are specifically associated with lupus nephritis, including *APOL1*, *ACE*, *ITGAM*, *HLA-DR* and multiple FCR genes.<sup>44</sup> An unbiased meta-analysis of genome-wide association screens comparing SLE patients with lupus nephritis to those without lupus nephritis identified a comprehensive list of nephritis-associated genes, including *PDGFRA*, *HLA-DR2*, *HLA-DR3*, *SLC5A11*, *ID4*, *HAS2* and

*SNTBI*.<sup>44</sup> Active research is underway to elucidate how these genes contribute to diseases. In cSLE patients with disease-onset before the age of 5, monogenic SLE should be investigated.<sup>45</sup> Most gene variants implicated in monogenic lupus relate to T cell and B cell tolerance, metabolism complement or type I interferon activation pathways.<sup>45</sup>

With the study of microRNAs, the role of epigenetics in lupus nephritis has been increasingly recognized.<sup>46,47</sup> A total of 171 circRNAs with 2-fold differential expression, including 142 upregulated and 29 downregulated circRNAs, were identified in renal biopsies from lupus nephritis patients compared with normal kidney specimens.<sup>48</sup> An increase in renal circHLA-C and a decrease in miR-150 has been observed in lupus nephritis when compared to healthy controls.<sup>48</sup> Increased circHLA-C has been observed in renal resident cells and urinary exosomes, and results in abnormal cell proliferation, inflammation, and fibrosis.<sup>47,49</sup> A positive correlation between miR-150 and renal chronicity index was identified.<sup>48</sup> circRNA\_002453 level was associated with complement levels, proteinuria and SLEDAI-2K scores in aSLE.<sup>50</sup> In cSLE, hsacirc0021372 and hsacirc0075699 levels are associated with C3 and C4 levels, and hsacirc0057762 level is positively associated with the SLEDAI-2K scores.<sup>51</sup>

The role of antibodies is well known in lupus nephritis. Double-stranded DNA (dsDNA) antibodies are specific to SLE and its presence scores in diagnosis criteria. Increase in dsDNA antibodies titers is associated with flares (renal and non-renal). Other autoantibodies, such as anti-C1q, anti-nucleosome, anti- $\alpha$  actinin, anticardiolipin (aCL), anti-ENO1 and anti-H2 IgG2, have been described in approximately 30% in SLE patients and may coexist with dsDNA antibodies. The association of these antibodies with clinical manifestations is still not elucidated. Circulating levels of anti-ENO1 and anti-Histone 2 A antibodies have been shown to reduce with treatment and may be a reliable marker of the effectiveness of therapy. However, they do not predict renal outcome.<sup>52</sup>

Uncontrolled activation of the complement system is associated with renal inflammation and damage. In addition to the classical pathway, the role of alternative and lectin pathway in the development of acute and chronic kidney disease has been recognized.<sup>53,54</sup> Low complement is observed during SLE disease activity, independently of the presence of nephritis. Cell bound complement split products, such as erythrocyte-bound C4d levels, are elevated in lupus nephritis and deposition in renal peritubular capillaries predicts a worse renal prognosis.<sup>55</sup>

Dysregulation of a wide range of immune system elements is observed in lupus nephritis.<sup>47</sup>

The presence of tissue inflammation increases the production of medullar and extramedullar neutrophils and is involved in endothelial and tissue damage.<sup>56</sup> Neutrophils releases greater amounts of High Mobility Group Box 1 (HMGB1) protein in SLE patients' comparison to healthy controls. HMGB1 activates multiple inflammatory cells and is associated with lupus nephritis pathogenesis.<sup>57</sup> In addition, neutrophils from SLE patients have an increased capacity to undergo NETosis.<sup>58</sup> NETs are also a source of extracellular HMGB1 and that the amount of HMGB1 in SLE NETs correlates with the severity of lupus nephritis.<sup>59</sup> NET remnants (Elastase-DNA and HMGB1-DNA complexes) are associated with proliferative lupus nephritis. Higher levels of baseline NET remnants are associated with higher odds of not achieving complete remission and of progressing to severe renal impairment 24 months after a renal flare.<sup>60</sup>

Infiltrating macrophages, both in glomeruli and in tubule-Interstitial, undergo a phenotypic change through NLRP3 inflammasome activation in lupus nephritis, and are responsible for antigen presentation and complement secretion. The number of infiltrating macrophages correlates with type I interferon activation in transcriptomic studies.<sup>61-63</sup>

Monocyte chemoattractant protein 1 (MCP-1), promotes monocyte migration to the kidney, can be measured in the urine and has been shown to be a biomarker for the diagnosis of lupus nephritis independently of age of disease-onset.<sup>64</sup>

In the peripheral blood of SLE patients with active nephritis an increased ratio of T follicular helper (TFH)/TREG has been observed.<sup>65</sup> A TFH1 cell infiltration has also been observed in the pathogenesis of lupus nephritis.<sup>66</sup>

## Diagnosis

SLE treatment guidelines strongly recommend timely recognition and treatment of renal involvement.<sup>67-69</sup> Early recognition and appropriate management of lupus nephritis are associated with better renal outcomes and reduced mortality over time.<sup>70</sup> In cohort studies, hypertension, male sex, low circulating C3, low albumin levels, dyslipidemia, presence of proteinuria, increased serum creatinine, dysmorphic hematuria, neutropenia, and higher SLEDAI or ACR scores have been identified as risk factors for lupus nephritis in cSLE.<sup>14,20,71-76</sup> In clinical practice, cSLE patients should be followed regularly with blood pressure monitoring, urine sediment analysis, quantification of proteinuria (spot protein creatinine ratio, dipstick or 24-hour urine protein), serum creatinine, estimated glomerular filtration rate (GFR), dsDNA

antibodies and complement levels (C3 and C4) to identify renal involvement early.<sup>67,77</sup> However, clinical examination and laboratory findings are not reliable enough to reflect the severity of renal disease. Renal biopsy is essential to establish the diagnosis and characterize disease severity, which is needed to guide treatment.<sup>68</sup>

In patients with cSLE, it is also important to exclude orthostatic or postural proteinuria as the cause of proteinuria, because orthostatic proteinuria is the most common cause of proteinuria in adolescents.<sup>69,78</sup> Kidney biopsy remains the gold standard for diagnosis of lupus nephritis in cSLE<sup>68</sup> and is indicated in cSLE patients who have renal function loss or sustained proteinuria exceeding 0.5 grams in twenty-four hours.<sup>77</sup> In a study that included 222 patients with SLE, low-grade proteinuria (<0.5 grams in twenty-four hours) in the presence of dysmorphic hematuria was shown to be associated with active lupus nephritis on histology.<sup>79</sup>

Silent lupus nephritis is defined as the presence of renal pathology in SLE patients with normal urinalysis findings.<sup>36</sup> This is a challenge in clinical practice since renal biopsy is generally indicated in cSLE patients with abnormal urinalysis.<sup>80,81</sup> Although most silent lupus nephritis patients present class I and II nephritis, a significant number present class III or IV on renal biopsy and have an increased risk of ESRD. Low complement levels have been shown to be associated with proliferative lupus nephritis, independently of the presence of urinalysis abnormalities.<sup>36,82</sup> Therefore, the presence of low complement levels in cSLE patients with normal urinalysis should alert to the possibility of the presence of silent lupus nephritis.<sup>36,82</sup>

### Renal Biopsy and Histopathological Scoring

Renal biopsy is a relatively safe procedure and in many settings is done percutaneously, guided by ultrasound.<sup>83</sup> It is important to have an experienced pathologist in lupus nephritis to examine the biopsy specimen.<sup>84</sup> Based on the histological findings, the classification system of the ISN/RPS recognizes six classes of nephritis, which are associated with response to treatment and prognosis, including long-term renal outcome (Table 2).<sup>85,86</sup>

Predominant class III/IV renal pathology was found in the majority (75%) of patients with low-grade proteinuria (<0.5 grams in twenty-four hours) and dysmorphic hematuria. Silent lupus nephritis, which is defined as the presence of active nephritis by histology in the absence of any urine sediment abnormality, is comprised class I or II nephritis in the majority, and class III/IV in the minority (20%).<sup>24,88</sup>

Renal biopsies should be scored for components of disease activity and chronicity. Components of disease activity include endocapillary hypercellularity, neutrophils or karyorrhexis, fibrinoid necrosis, fibrinoid necrosis, hyaline deposits (wireloops or hyaline thrombi), cellular or fibrocellular and/or interstitial inflammation. Chronicity components include glomerular sclerosis (segmental, global), fibrous crescents, interstitial fibrosis and/or tubular atrophy. Scores range from 0 to 24 for disease activity and 0–12 for chronicity. The score takes into account the extent of glomerular involvement,

**Table 2** ISN/RPS Classification and Frequency of Lupus Nephritis in Children and Adolescents. Adapted from<sup>17,20,84–87</sup>

ISN/RPS Classification	Description	Frequency in cSLE
Class I	immunocomplex deposition (immunofluorescence and electron microscopy) without concomitant light microscopic alterations	1–16%
Class II	Class I, in addition to mesangial hypercellularity ( $\geq 3$ cells surrounded by the matrix)	
Class III	<50% of glomeruli with focal lupus nephritis (subendothelial immunocomplex deposition with endocapillary hypercellularity or inactive glomerular scars). Focal or diffuse mesangial immunocomplex deposition can be present	28–34%
Class IV	$\geq 50\%$ of glomeruli with focal lupus nephritis; presence of subendothelial immunocomplex deposition with endocapillary hypercellularity or inactive glomerular scars. Focal or diffuse mesangial immunocomplex deposition can be present	36–41%
Class V	Subepithelial immunocomplex deposition	11–25%
Class VI	$\geq 90\%$ of evaluated glomeruli show glomerulosclerosis, determined by a combination of glomerular, vascular, and tubulointerstitial injury	~1%

categorized as less than 25%, 25–50% or more than 50%.<sup>86</sup> In a validation study with cSLE patients, 10% threshold for fibrous crescents better discriminated kidney disease outcomes compared to the thresholds validated in adults with SLE.<sup>89–94</sup> In particular, 10% threshold for fibrous crescents was predictive of kidney failure and glomerular filtration rate at one year follow-up in cSLE.<sup>91</sup> The addition of 10% threshold for cellular crescents did not predict kidney disease outcomes.<sup>91</sup> Items not included in the scoring system are collapsing lupus glomerulopathy, podocytopathy and vascular lesions. Renal vascular lesions are observed in up to 20% of cSLE biopsies and associated with lower estimated glomerular filtration rate and greater renal damage.<sup>37</sup>

Electron microscopy can be used to identify the location of immune deposits and extent and severity of podocyte injury.<sup>86</sup>

There remains no consensus on repeated biopsy in cSLE in clinical practice. Approximately twenty-five percent of pediatric nephrologists and rheumatologists who treat cSLE recommend repeat kidney biopsy when patients with proliferative lupus nephritis fail to achieve a complete clinical response upon completion of induction therapy.<sup>83</sup> However, far fewer pediatric rheumatologists and nephrologists perform repeat biopsy after sustained remission to support their decision to withdraw immunosuppression.<sup>83</sup>

### Biomarkers

Traditional biomarkers for lupus nephritis (C3, dsDNA, proteinuria, anti-C1q antibodies, isolated dysmorphic hematuria) fail to accurately predict renal flares once they are corrected for extra-renal disease activity.<sup>95–100</sup> Even the routinely used measures of kidney function, urinary protein excretion and dysmorphic hematuria, are imprecise in determining flare and disease remission.<sup>75,101</sup> Although not useful for detecting renal flares, C3 and C4 demonstrated a good discriminative ability to detect proliferative nephritis in cSLE [ROC curve (C3 = 0.78, C4 = 0.78)].<sup>82</sup>

A urine biomarker panel consisting of 6 urine proteins (neutrophil gelatinase-associated lipocalin, monocyte chemoattractant protein-1, kidney injury molecule-1, ceruloplasmin, adiponectin, and hemopexin) has been developed and validated.<sup>102,103</sup> Based on the concentrations of these biomarkers, the Renal Activity Index for Lupus (RAIL) can be calculated for adults and pediatric patients. Higher scores on RAIL are associated with high inflammation on renal biopsy.<sup>102,103</sup> RAIL is also sensitive to change and, in cSLE, a decrease of 1 or greater is associated with complete response to induction therapy.<sup>104</sup> In addition, urinary levels of adiponectin and osteopontin predict damage originated from lupus nephritis with similar accuracy as the glomerular filtration rate.<sup>105</sup>

### Treatment

Lupus nephritis demands a therapeutic strategy that is individualized, based on patient presentation, renal function, class of nephritis, and extra-renal involvement. Up to date, the responsiveness to induction therapy, however, cannot be predicted by clinical or biochemical criteria.<sup>104,106</sup> Large-scale trials of nephritis in cSLE are lacking due to challenges in design and conduct of clinical trials for rare and highly complex pediatric diseases. Thus, management of lupus nephritis in cSLE relies on extrapolation from large-scale trials in adults and clinical experience.<sup>107</sup> Kidney Disease Improving Global Outcomes (KDIGO) guidelines were derived for aSLE nephritis and are often followed in cSLE.<sup>67</sup> The lack of guidelines for the treatment of child-onset proliferative lupus nephritis led to the development of induction therapy consensus treatment plans (CTPs) by the Childhood Arthritis and Rheumatology Research Alliance (CARRA).<sup>101</sup> Although the CTPs were not meant to serve as treatment guidelines because sufficient evidence regarding the best treatment for nephritis in cSLE is not available, they are applicable to a large proportion of patients with newly diagnosed proliferative nephritis in cSLE, and when widely utilized shall allow for the accumulation of data for comparative effectiveness analyses.

Immunosuppression is standard, with careful consideration of side effects. Treatment is often biphasic, consisting of induction therapy for acute control, followed by maintenance therapy. Induction therapy strategies used for nephritis in cSLE are supported by randomized controlled trials of nephritis treatment in aSLE.<sup>108,109</sup> Hydroxychloroquine (HCQ) should be added to treatment regime in all cSLE patients. Although often a flat dose of 5 mg/kg/day is recommended, current weight-based dosing paradigm for HCQ may result in suboptimal drug exposures, particularly for children with obesity.<sup>110</sup> A high interindividual variability in blood levels for the same administered dose of HCQ is observed.<sup>9,111</sup>



More than 80% of cSLE patients were in remission with HCQ blood levels  $\geq 750$  ng/mL, suggesting that this could be a reasonable therapeutic threshold in cSLE.<sup>111</sup> Longstanding HCQ treatment is associated with hyperpigmentation of skin, depending on drug dosage and treatment length.<sup>112,113</sup>

For induction of remission, studies of adults with lupus nephritis have demonstrated comparable efficacy and toxicity between intravenous cyclophosphamide at low-dose (500 mg IV pulse for 6 biweekly pulses) and high-dose (750 mg/m<sup>2</sup>/pulse up to a maximum of 1200 mg/pulse for 6 monthly pulses).<sup>109</sup> Additionally, renal outcomes were similar when comparing high-dose IV cyclophosphamide to mycophenolate mofetil (1000 mg/day up to 3000 mg/day) as induction therapy.<sup>108</sup> In cSLE, the recommended mycophenolate mofetil dose is 600mg/m<sup>2</sup>/dose twice a day up to a maximal dose of 300 mg/day as induction therapy, followed by 400mg/m<sup>2</sup>/dose twice a day as maintenance therapy.<sup>114</sup>

Tacrolimus (Tac) has been used in longterm observational studies in cSLE, mainly in Japan.<sup>115</sup> Induction therapy consisted in Tac (3 mg/day (0.03–0.075 mg/kg)) plus mizoribine (MZR) (150 mg/day once daily) in combination with prednisone for rapid tapering of the concomitantly administered PDN.<sup>115,116</sup> MZR is a selective inhibitor of inosine monophosphate dehydrogenase in the de novo purine synthesis pathway and acts in a manner similar to that of mycophenolate mofetil (MMF).<sup>115</sup> Long-term follow-up (5 and 10 years) has shown that Tac is safe and well tolerated. Low cytotoxicity and renal damage were observed. Despite the long follow-up, a small number of patients (<15) were included in the study.<sup>115,116</sup>

Belimumab has the potential to increase the chance of achieving complete renal response or primary efficacy renal response, and when compared to placebo it is associated with reduced risk of kidney failure and mortality in aSLE.<sup>117</sup> A phase-2, randomised, placebo-controlled, double-blind study demonstrated that belimumab intravenous pharmacokinetics and benefit–risk profile in cSLE is consistent with adult belimumab studies and the 10 mg/kg every 4 weeks dose is appropriate.<sup>118</sup> In cSLE, adding belimumab to standard of care, children had an equivalent renal remission rate and low adverse events.<sup>119</sup> Corticosteroid doses were significantly lower in the belimumab group, and no difference in renal flares was observed in both groups.<sup>119</sup>

In a small open-label study, multi-targeted induction and maintenance protocol based on intravenous pulse methylprednisolone, mycophenolate mofetil and cyclosporine showed a 75% remission rate and a 73% cumulative ten-year renal relapse-free survival.<sup>120,121</sup>

The efficacy of rituximab in SLE is not supported by randomized clinical studies in aSLE.<sup>122,123</sup> Despite the lack of approved use for children, it has been used off-label in hospitalized or severely ill patients with cSLE.<sup>124</sup> In a recent systematic review, renal involvement was the most frequent clinical manifestations associated with rituximab use in cSLE.<sup>124</sup> In real practice, adding rituximab to standard therapy has shown to reduce disease activity, improve renal outcome, and reduce flares and total corticosteroid dose with a favorable safety profile.<sup>124–130</sup>

Target of rapamycin (mTOR) inhibitors, especially sirolimus, has been used in refractory nephritis in cSLE. In a retrospective study of 32 cSLE patients, sirolimus (starting dose of 0.5 to 1 mg/m<sup>2</sup> daily, and further titrated to maintain a therapeutic range of 5 to 10 ng/mL at least 6 months) was associated with decreased disease activity and reduced prednisone dosage, with a favorable safety profile.<sup>131</sup> The most common clinical manifestations that led to sirolimus use were low complement (87%) and cytopenia (75%) and sirolimus was withdrawn owing to the development of lupus nephritis.<sup>131</sup> Further studies in cSLE nephritis are warranted.

Leflunomide has been used as second-line therapy in aSLE patients with lupus nephritis.<sup>67</sup> Although leflunomide has a good safety profile in adults with promising results in Chinese patients, no data in cSLE are available so far.<sup>132</sup>

Data suggest that high dose intravenous corticosteroid rather than lower potency oral corticosteroids have the potential to reduce the number of plasmacytoid dendritic cells and consequently eliminate the interferon alpha gene expression signature in SLE.<sup>133</sup> High-dose intravenous corticosteroid is used in induction therapy regimens. Corticosteroid doses reflect the physician experience, although a constant search for the lowest dose and duration is recommended.<sup>101</sup> Corticosteroid toxicity is a major concern in cSLE patients and a predictor of damage accrual.<sup>134</sup> The burden of corticosteroid-related morbidity remains high, especially when considering blood pressure, weight, sleep, and growth restriction and can be assessed using a standardized instrument.<sup>135</sup> There is no consensus on corticosteroid tapering regimen, however achieving 10–20 mg prednisone or equivalent daily by competition of the induction phase (24 weeks or 6 months) is a common goal amongst CARRA consensus treatment plans.<sup>101</sup>

Chimeric antigen receptor (CAR) T-cell therapy has garnered significant attention for its promising potential in SLE. So far, 2 cSLE patients with refractory disease and with nephritis, have been reported showing potential therapeutic efficacy and safety in a follow-up of 5 months period.<sup>136</sup>

### Chronic Kidney Disease (CKD)

Chronic kidney disease (CKD) is defined by the presence of either kidney damage or decreased kidney function for a minimum of three months. Decreased kidney function is determined by a glomerular filtration rate (GFR) persistently below 60 mL/min/1.73 m<sup>2</sup> (classified as GFR categories G3a-G5).

In a large-scale study of 1528 cSLE patients from Brazil, a country known for its multiethnic population, only a small number of patients with cSLE-developed stages III–V CKD, but with noteworthy frequencies of dialysis and kidney transplantation. Data also revealed that cSLE patients who had hypertension, biopsy-proven proliferative nephritis, and did not use antimalarials such as hydroxychloroquine exhibited higher hazard rates toward CKD progression.<sup>15,18</sup> While potential bias due to the lack of kidney biopsies should be acknowledged, the findings warrant consideration in future analyses. Importantly, while novel therapeutic approaches for lupus nephritis are being investigated, preserving renal function remains paramount. Rigorous management of CKD is thus essential, including monitoring and control of renal function, proteinuria, anemia, and blood pressure.<sup>137,138</sup>

### Conclusion

Nephritis is among one of the most frequent manifestations in cSLE, more often occurring within the first two years of diagnosis and associated with increased morbidity and mortality. Challenges in conducting studies in rare and highly complex pediatric diseases such as nephritis in cSLE have made progress challenging. However, major progress has been made in the past several years, including the development of pediatric-specific consensus treatment plans for proliferative nephritis, adjustment of the proportion of fibrous crescents when scoring nephritis in cSLE to better discriminated kidney disease outcomes, and the development of non-invasive biomarkers to identify renal disease activity and damage. Late diagnosis and corticosteroid toxicity remain a significant burden and a major risk factor for morbidity and mortality. Accurate biomarkers should foster multicenter studies and help identify new treatment approaches to improve outcomes in cSLE nephritis.

### Funding

Grants: Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq 305981/2023-4).

### Disclosure

The authors report no conflicts of interest in this work.

### References

- Couture J, Silverman ED. Update on the pathogenesis and treatment of childhood-onset systemic lupus erythematosus. *Curr Opin Rheumatol*. 2016;28(5):488–496. doi:10.1097/BOR.0000000000000317
- Kamphuis S, Silverman ED. Prevalence and burden of pediatric-onset systemic lupus erythematosus. *Nat Rev Rheumatol*. 2010;6(9):538–546. doi:10.1038/nrrheum.2010.121
- Mackie FE, Kainer G, Adib N, et al. The national incidence and clinical picture of SLE in children in Australia - a report from the Australian Paediatric Surveillance Unit. *Lupus*. 2015;24(1):66–73. doi:10.1177/0961203314552118
- Hiraki LT, Feldman CH, Liu J, et al. Prevalence, incidence, and demographics of systemic lupus erythematosus and lupus nephritis from 2000 to 2004 among children in the US Medicaid beneficiary population. *Arthritis Rheum*. 2012;64(8):2669–2676. doi:10.1002/art.34472
- Das Chagas Medeiros MM, Bezerra MC, Braga FN, et al. Clinical and immunological aspects and outcome of a Brazilian cohort of 414 patients with systemic lupus erythematosus (SLE): comparison between childhood-onset, adult-onset, and late-onset SLE. *Lupus*. 2016;25(4):355–363. doi:10.1177/0961203315606983
- Tarr T, Derfalvi B, Gyori N, et al. Similarities and differences between pediatric and adult patients with systemic lupus erythematosus. *Lupus*. 2015;24(8):796–803. doi:10.1177/0961203314563817
- Livingston B, Bonner A, Pope J. Differences in clinical manifestations between childhood-onset lupus and adult-onset lupus: a meta-analysis. *Lupus*. 2011;20(13):1345–1355. doi:10.1177/0961203311416694
- Peyronel F, Rossi GM, Palazzini G, et al. Early-onset lupus nephritis. *Clin Kidney J*. 2024;17(8):sfae212. doi:10.1093/ckj/sfae212
- Vazzana KM, Daga A, Goilav B, et al. Principles of pediatric lupus nephritis in a prospective contemporary multi-center cohort. *Lupus*. 2021;30(10):1660–1670. doi:10.1177/09612033211028658

10. Harry O, Yasin S, Brunner H. Childhood-Onset Systemic Lupus Erythematosus: a Review and Update. *J Pediatr.* 2018;196:22–30e2. doi:10.1016/j.jpeds.2018.01.045
11. Hiraki LT, Benseler SM, Tyrrell PN, Hebert D, Harvey E, Silverman ED. Clinical and laboratory characteristics and long-term outcome of pediatric systemic lupus erythematosus: a longitudinal study. *J Pediatr.* 2008;152(4):550–556. doi:10.1016/j.jpeds.2007.09.019
12. Font J, Cervera R, Espinosa G, et al. Systemic lupus erythematosus (SLE) in childhood: analysis of clinical and immunological findings in 34 patients and comparison with SLE characteristics in adults. *Ann Rheum Dis.* 1998;57(8):456–459. doi:10.1136/ard.57.8.456
13. Hafeez F, Tarar AM, Saleem R. Lupus nephritis in children. *J Coll Physicians Surg Pak.* 2008;18(1):17–21.
14. Baqi N, Moazami S, Singh A, Ahmad H, Balachandra S, Tejani A. Lupus nephritis in children: a longitudinal study of prognostic factors and therapy. *J Am Soc Nephrol.* 1996;7(6):924–929. doi:10.1681/ASN.V76924
15. McCurdy DK, Lehman TJ, Bernstein B, et al. Lupus nephritis: prognostic factors in children. *Pediatrics.* 1992;89(2):240–246. doi:10.1542/peds.89.2.240
16. Pereira T, Abitbol CL, Seeherunvong W, et al. Three decades of progress in treating childhood-onset lupus nephritis. *Clin J Am Soc Nephrol.* 2011;6(9):2192–2199. doi:10.2215/CJN.00910111
17. De Mutiis C, Wenderfer SE, Basu B, et al. International cohort of 382 children with lupus nephritis - presentation, treatment and outcome at 24 months. *Pediatr Nephrol.* 2023;38(11):3699–3709. doi:10.1007/s00467-023-06018-5
18. Sakamoto AP, Silva CA, Islabao AG, et al. Chronic kidney disease in patients with childhood-onset systemic lupus erythematosus. *Pediatr Nephrol.* 2023;38(6):1843–1854. doi:10.1007/s00467-022-05811-y
19. Biswas D, Dasgupta D, Pal P, Sinha R. Presentation and outcome of pediatric lupus nephritis from a large single centre contemporary cohort in Eastern India. *Lupus.* 2023;32(12):1440–1446. doi:10.1177/09612033231202843
20. Smitherman EA, Chahine RA, Beukelman T, et al. Childhood-Onset Lupus Nephritis in the Childhood Arthritis and Rheumatology Research Alliance Registry: short-Term Kidney Status and Variation in Care. *Arthritis Care Res.* 2023;75(7):1553–1562. doi:10.1002/acr.25002
21. Cervera R, Khamashta MA, Font J, et al. Morbidity and mortality in systemic lupus erythematosus during a 10-year period: a comparison of early and late manifestations in a cohort of 1,000 patients. *Medicine.* 2003;82(5):299–308. doi:10.1097/01.md.0000091181.93122.55
22. Mejia-Vilet JM, Cordova-Sanchez BM, Uribe-Urbe NO, Correa-Rotter R, Morales-Buenrostro LE. Prognostic significance of renal vascular pathology in lupus nephritis. *Lupus.* 2017;26(10):1042–1050. doi:10.1177/0961203317692419
23. Barber C, Herzenberg A, Aghdassi E, et al. Evaluation of clinical outcomes and renal vascular pathology among patients with lupus. *Clin J Am Soc Nephrol.* 2012;7(5):757–764. doi:10.2215/CJN.02870311
24. Wakasugi D, Gono T, Kawaguchi Y, et al. Frequency of class III and IV nephritis in systemic lupus erythematosus without clinical renal involvement: an analysis of predictive measures. *J Rheumatol.* 2012;39(1):79–85. doi:10.3899/jrheum.110532
25. Hanly JG, O’Keeffe AG, Su L, et al. The frequency and outcome of lupus nephritis: results from an international inception cohort study. *Rheumatology (Oxford).* 2016;55(2):252–262. doi:10.1093/rheumatology/kev311
26. Mongkolchaiarunya J, Wongthanee A, Kasitanon N, Louthrenoo W. Comparison of Clinical Features, Treatment and Outcomes of Lupus Nephritis Between Patients With Late- and Early-Onset Systemic Lupus Erythematosus: a Controlled Study. *J Clin Med Res.* 2024;16(2–3):106–117. doi:10.14740/jocmr5097
27. Sassi RH, Hendlar JV, Piccoli GF, et al. Age of onset influences on clinical and laboratory profile of patients with systemic lupus erythematosus. *Clin Rheumatol.* 2017;36(1):89–95. doi:10.1007/s10067-016-3478-4
28. Watson L, Leone V, Pilkington C, et al. Disease activity, severity, and damage in the UK Juvenile-Onset Systemic Lupus Erythematosus Cohort. *Arthritis Rheum.* 2012;64(7):2356–2365. doi:10.1002/art.34410
29. Samanta M, Nandi M, Mondal R, et al. Childhood lupus nephritis: 12 years of experience from a developing country’s perspective. *Eur J Rheumatol.* 2017;4(3):178–183. doi:10.5152/eurjrheum.2017.16117
30. Groot N, Shaikhani D, Teng YKO, et al. Long-Term Clinical Outcomes in a Cohort of Adults With Childhood-Onset Systemic Lupus Erythematosus. *Arthritis Rheumatol.* 2019;71(2):290–301. doi:10.1002/art.40697
31. Hari P, Bagga A, Mahajan P, Dinda A. Outcome of lupus nephritis in Indian children. *Lupus.* 2009;18(4):348–354. doi:10.1177/0961203308097570
32. Taheri S, Beiraghdar F. Lupus nephritis in Iranian children: a review of 60 patients. *Ren Fail.* 2011;33(5):499–505. doi:10.3109/0886022X.2011.573897
33. Wong SN, Tse KC, Lee TL, et al. Lupus nephritis in Chinese children--a territory-wide cohort study in Hong Kong. *Pediatr Nephrol.* 2006;21(8):1104–1112. doi:10.1007/s00467-006-0052-3
34. Vachvanichsanong P, Dissaneewate P, McNeil E. Diffuse proliferative glomerulonephritis does not determine the worst outcome in childhood-onset lupus nephritis: a 23-year experience in a single centre. *Nephrol Dial Transplant.* 2009;24(9):2729–2734. doi:10.1093/ndt/gfp173
35. Chang JC, Liu JP, Berbert LM, et al. Racial and Ethnic Composition of Populations Served by Freestanding Children’s Hospitals and Disparities in Outcomes of Pediatric Lupus. *Arthritis Care Res.* 2024;76(7):926–935. doi:10.1002/acr.25314
36. Wakiguchi H, Takei S, Kubota T, Miyazono A, Kawano Y. Treatable renal disease in children with silent lupus nephritis detected by baseline biopsy: association with serum C3 levels. *Clin Rheumatol.* 2017;36(2):433–437. doi:10.1007/s10067-016-3491-7
37. Lin YK, EY-h C, Y-f M, et al. Renal vascular lesions in Childhood-onset Lupus Nephritis. *Pediatric Nephrology.* 2024;40:131–141. doi:10.21203/rs.3.rs-3988068/v1
38. Mohan C, Zhang T, Putterman C. Pathogenic cellular and molecular mediators in lupus nephritis. *Nat Rev Nephrol.* 2023;19(8):491–508. doi:10.1038/s41581-023-00722-z
39. Postal M, Vivaldo JF, Fernandez-Ruiz R, Paredes JL, Appenzeller S, Niewold TB. Type I interferon in the pathogenesis of systemic lupus erythematosus. *Curr Opin Immunol.* 2020;67:87–94. doi:10.1016/j.coi.2020.10.014
40. Londe AC, Fernandez-Ruiz R, Julio PR, Appenzeller S, Niewold TB. Type I Interferons in Autoimmunity: implications in Clinical Phenotypes and Treatment Response. *J Rheumatol.* 2023;50(9):1103–1113. doi:10.3899/jrheum.2022-0827
41. Iwamoto T, Dorschner JM, Selvaraj S, et al. High Systemic Type I Interferon Activity Is Associated With Active Class III/IV Lupus Nephritis. *J Rheumatol Apr.* 2022;49(4):388–397. doi:10.3899/jrheum.210391



42. Arriens C, Raja Q, Husain SA, et al. Increased risk of progression to lupus nephritis for lupus patients with elevated interferon signature. *Arthritis Rheumatol.* 2019;71(suppl 10):411–419. doi:10.1002/art.40724
43. Zickert A, Oke V, Parodis I, Svenungsson E, Sundstrom Y, Gunnarsson I. Interferon (IFN)-lambda is a potential mediator in lupus nephritis. *Lupus Sci Med.* 2016;3(1):e000170. doi:10.1136/lupus-2016-000170
44. Song K, Liu L, Zhang X, Chen X. An update on genetic susceptibility in lupus nephritis. *Clin Immunol.* 2020;210:108272. doi:10.1016/j.clim.2019.108272
45. Qin Y, Ma J, Vinuesa CG. Monogenic lupus: insights into disease pathogenesis and therapeutic opportunities. *Curr Opin Rheumatol.* 2024;36(3):191–200. doi:10.1097/BOR.0000000000001008
46. So BYF, Yap DYH, Chan TM. MicroRNAs in Lupus Nephritis-Role in Disease Pathogenesis and Clinical Applications. *Int J Mol Sci.* 2021;22(19):10737. doi:10.3390/ijms221910737
47. Roveta A, Parodi EL, Brezzi B, et al. Lupus Nephritis from Pathogenesis to New Therapies: an Update. *Int J Mol Sci.* 2024;25(16):8981. doi:10.3390/ijms25168981
48. Luan J, Jiao C, Kong W, et al. circHLA-C Plays an Important Role in Lupus Nephritis by Sponging miR-150. *Mol Ther Nucleic Acids.* 2018;10:245–253. doi:10.1016/j.omtn.2017.12.006
49. Xu N, Liu J, Li X. Lupus nephritis: the regulatory interplay between epigenetic and MicroRNAs. *Front Physiol.* 2022;13:925416. doi:10.3389/fphys.2022.925416
50. Ouyang Q, Huang Q, Jiang Z, Zhao J, Shi GP, Yang M. Using plasma circRNA\_002453 as a novel biomarker in the diagnosis of lupus nephritis. *Mol Immunol.* 2018;101:531–538. doi:10.1016/j.molimm.2018.07.029
51. Li S, Zhang J, Tan X, et al. Microarray expression profile of circular RNAs and mRNAs in children with systemic lupus erythematosus. *Clin Rheumatol.* 2019;38(5):1339–1350. doi:10.1007/s10067-018-4392-8
52. Bruschi M, Angeletti A, Prunotto M, et al. A critical view on autoantibodies in lupus nephritis: concrete knowledge based on evidence. *Autoimmun Rev.* 2024;23(5):103535. doi:10.1016/j.autrev.2024.103535
53. Fernandez-Ruiz R, Belmont HM. The role of anticomplement therapy in lupus nephritis. *Transl Res.* 2022;245:1–17. doi:10.1016/j.trsl.2022.02.001
54. Li NL, Birmingham DJ, Rovin BH. Expanding the Role of Complement Therapies: the Case for Lupus Nephritis. *J Clin Med.* 2021;10(4):626. doi:10.3390/jcm10040626
55. Qin S, Wang X, Wang J, Wu H. Complement C4d as a biomarker for systemic lupus erythematosus and lupus nephritis. *Lupus.* 2024;33(2):111–120. doi:10.1177/09612033231226351
56. Zervopoulou E, Grigoriou M, Doulas SA, et al. Enhanced medullary and extramedullary granulopoiesis sustain the inflammatory response in lupus nephritis. *Lupus Sci Med.* 2024;11(1):e001110. doi:10.1136/lupus-2023-001110
57. Harris HE, Andersson U, Pisetsky DS. HMGB1: a multifunctional alarmin driving autoimmune and inflammatory disease. *Nat Rev Rheumatol.* 2012;8(4):195–202. doi:10.1038/nrrheum.2011.222
58. Garcia-Romo GS, Caielli S, Vega B, et al. Netting neutrophils are major inducers of type I IFN production in pediatric systemic lupus erythematosus. *Sci Transl Med.* 2011;3(73):73ra20. doi:10.1126/scitranslmed.3001201
59. Whittall-García L, Torres-Ruiz J, Zentella-Dehesa A, et al. Neutrophil extracellular traps are a source of extracellular HMGB1 in lupus nephritis: associations with clinical and histopathological features. *Lupus.* 2019;28(13):1549–1557. doi:10.1177/0961203319883936
60. Whittall-García LP, Naderinabi F, Gladman DD, et al. Circulating neutrophil extracellular trap remnants as a biomarker to predict outcomes in lupus nephritis. *Lupus Sci Med.* 2024;11(1):e001038. doi:10.1136/lupus-2023-001038
61. Kwant LE, Vegting Y, Tsang ASMWP, et al. Macrophages in Lupus Nephritis: exploring a potential new therapeutic avenue. *Autoimmun Rev.* 2022;21(12):103211. doi:10.1016/j.autrev.2022.103211
62. Wei S, Shen H, Zhang Y, et al. Integrative analysis of single-cell and bulk transcriptome data reveal the significant role of macrophages in lupus nephritis. *Arthritis Res Ther.* 2024;26(1):84. doi:10.1186/s13075-024-03311-y
63. Tian J, Chang S, Wang J, et al. SIP/S1PR1 axis promotes macrophage M1 polarization through NLRP3 inflammasome activation in Lupus nephritis. *Mol Immunol.* 2023;160:55–66. doi:10.1016/j.molimm.2023.06.006
64. Goilav B, Putterman C, Rubinstein TB. Biomarkers for kidney involvement in pediatric lupus. *Biomarker Med.* 2015;9(6):529–543. doi:10.2217/bmm.15.25
65. Xu B, Wang S, Zhou M, et al. The ratio of circulating follicular T helper cell to follicular T regulatory cell is correlated with disease activity in systemic lupus erythematosus. *Clin Immunol.* 2017;183:46–53. doi:10.1016/j.clim.2017.07.004
66. Satoh-Kanda Y, Nakayamada S, Kubo S, et al. Modifying T cell phenotypes using TYK2 inhibitor and its implications for the treatment of systemic lupus erythematosus. *RMD Open.* 2024;10(2):e003991. doi:10.1136/rmdopen-2023-003991
67. BH Rovin, IM Ayoub, TM Chan. Kidney Disease: improving Global Outcomes Lupus Nephritis Work G. KDIGO 2024 Clinical Practice Guideline for the management of LUPUS NEPHRITIS. *Kidney Int.* 2024;105(1S):S1–S69. doi:10.1016/j.kint.2023.09.002
68. Smith EMD, Aggarwal A, Ainsworth J, et al. Towards development of treat to target (T2T) in childhood-onset systemic lupus erythematosus: pReS-endorsed overarching principles and points-to-consider from an international task force. *Ann Rheum Dis.* 2023;82(6):788–798. doi:10.1136/ard-2022-223328
69. Groot N, de Graeff N, Marks SD, et al. European evidence-based recommendations for the diagnosis and treatment of childhood-onset lupus nephritis: the SHARE initiative. *Ann Rheum Dis.* 2017;76(12):1965–1973. doi:10.1136/annrheumdis-2017-211898
70. Houssiau FA, Vasconcelos C, D’Cruz D, et al. Early response to immunosuppressive therapy predicts good renal outcome in lupus nephritis: lessons from long-term followup of patients in the Euro-Lupus Nephritis Trial. *Arthritis Rheum.* 2004;50(12):3934–3940. doi:10.1002/art.20666
71. Appel AE, Sablay LB, Golden RA, Barland P, Grayzel AI, Bank N. The effect of normalization of serum complement and anti-DNA antibody on the course of lupus nephritis: a two year prospective study. *Am J Med.* 1978;64(2):274–283. doi:10.1016/0002-9343(78)90056-6
72. Bastian HM, Roseman JM, McGwin Jr G, et al. Systemic lupus erythematosus in three ethnic groups. XII. Risk factors for lupus nephritis after diagnosis. *Lupus.* 2002;11(3):152–160. doi:10.1191/0961203302lu1580a
73. Hsu TC, Yang YH, Wang LC, et al. Risk factors for subsequent lupus nephritis in patients with juvenile-onset systemic lupus erythematosus: a retrospective cohort study. *Pediatr Rheumatol Online J.* 2023;21(1):28. doi:10.1186/s12969-023-00806-x

74. Smith EMD, Yin P, Jorgensen AL, Beresford MW. Clinical predictors of active LN development in children - evidence from the UK JSLE Cohort Study. *Lupus*. 2018;27(13):2020–2028. doi:10.1177/0961203318801526
75. Sule SD, Moodalbail DG, Burnham J, Fivush B, Furth SL. Predictors of kidney disease in a cohort of pediatric patients with lupus. *Lupus*. 2015;24(8):862–868. doi:10.1177/0961203315570162
76. Liu J, Song W, Cui D. Relationship between Blood Lipid Profiles and Risk of Lupus Nephritis in Children. *Int J Clin Pract*. 2022;2022(1):6130774. doi:10.1155/2022/6130774
77. Mina R, Harris JG, Klein-Gitelman MS, et al. Initial Benchmarking of the Quality of Medical Care in Childhood-Onset Systemic Lupus Erythematosus. *Arthritis Care Res*. 2016;68(2):179–186. doi:10.1002/acr.22666
78. Sebestyen JF, Alon US. The teenager with asymptomatic proteinuria: think orthostatic first. *Clin Pediatr*. 2011;50(3):179–182. doi:10.1177/0009922810380904
79. De Rosa M, Rocha AS, De Rosa G, Dubinsky D, Almaani SJ, Rovin BH. Low-Grade Proteinuria Does Not Exclude Significant Kidney Injury in Lupus Nephritis. *Kidney Int Rep*. 2020;5(7):1066–1068. doi:10.1016/j.ekir.2020.04.005
80. Hollander MC, Sage JM, Greenler AJ, et al. International consensus for provisions of quality-driven care in childhood-onset systemic lupus erythematosus. *Arthritis Care Res*. 2013;65(9):1416–1423. doi:10.1002/acr.21998
81. Bertsias GK, Tektonidou M, Amoura Z, et al. Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. *Ann Rheum Dis*. 2012;71(11):1771–1782. doi:10.1136/annrheumdis-2012-201940
82. Mannemuddhu SS, Shoemaker LR, Bozorgmehri S, et al. Does kidney biopsy in pediatric lupus patients “complement” the management and outcomes of silent lupus nephritis? Lessons learned from a pediatric cohort. *Pediatr Nephrol*. 2023;38(8):2669–2678. doi:10.1007/s00467-022-05859-w
83. Wenderfer SE, Lane JC, Shatat IF, von Scheven E, Ruth NM. Practice patterns and approach to kidney biopsy in lupus: a collaboration of the Midwest Pediatric Nephrology Consortium and the Childhood Arthritis and Rheumatology Research Alliance. *Pediatr Rheumatol Online J*. 2015;13(1):26. doi:10.1186/s12969-015-0024-x
84. Weening JJ, D’Agati VD, Schwartz MM, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. *J Am Soc Nephrol*. 2004;15(2):241–250. doi:10.1097/01.asn.0000108969.21691.5d
85. Marks SD, Sebire NJ, Pilkington C, Tullus K. Clinicopathological correlations of paediatric lupus nephritis. *Pediatr Nephrol*. 2007;22(1):77–83. doi:10.1007/s00467-006-0296-y
86. Bajema IM, Wilhelmus S, Alpers CE, et al. Revision of the International Society of Nephrology/Renal Pathology Society classification for lupus nephritis: clarification of definitions, and modified National Institutes of Health activity and chronicity indices. *Kidney Int*. 2018;93(4):789–796. doi:10.1016/j.kint.2017.11.023
87. Park E, Jung J, Min J, et al. Long-term outcomes and associated prognostic risk factors of childhood-onset lupus nephritis. *Kidney Res Clin Pract*. 2023;2023:1–7. doi:10.23876/j.krcp.23.032
88. Zabaleta-Lanz ME, Munoz LE, Tapanes FJ, et al. Further description of early clinically silent lupus nephritis. *Lupus*. 2006;15(12):845–851. doi:10.1177/0961203306070002
89. Hachiya A, Karasawa M, Imaizumi T, et al. The ISN/RPS 2016 classification predicts renal prognosis in patients with first-onset class III/IV lupus nephritis. *Sci Rep*. 2021;11(1):1525. doi:10.1038/s41598-020-78972-1
90. Krassanairawiwong K, Charoenpitakchai M, Supasynhd O, Satirapoj B. Revised ISN/RPS 2018 classification of lupus renal pathology predict clinical remission. *Int Urol Nephrol*. 2021;53(7):1391–1398. doi:10.1007/s12555-020-02732-3
91. Patel P, de Guzman M, Hicks MJ, et al. Utility of the 2018 revised ISN/RPS thresholds for glomerular crescents in childhood-onset lupus nephritis: a Pediatric Nephrology Research Consortium study. *Pediatr Nephrol*. 2022;37(12):3139–3145. doi:10.1007/s00467-022-05524-2
92. Tao J, Wang H, Yu XJ, et al. A Validation of the 2018 Revision of International Society of Nephrology/Renal Pathology Society Classification for Lupus Nephritis: a Cohort Study from China. *Am J Nephrol*. 2020;51(6):483–492. doi:10.1159/000507213
93. Umeda R, Ogata S, Hara S, et al. Comparison of the 2018 and 2003 International Society of Nephrology/Renal Pathology Society classification in terms of renal prognosis in patients of lupus nephritis: a retrospective cohort study. *Arthritis Res Ther*. 2020;22(1):260. doi:10.1186/s13075-020-02358-x
94. Wang H, Gao Y, Ma Y, et al. Performance of the 2019 EULAR/ACR systemic lupus erythematosus classification criteria in a cohort of patients with biopsy-confirmed lupus nephritis. *Lupus Sci Med*. 2021;8(1). doi:10.1136/lupus-2020-000458
95. Esdaile JM, Joseph L, Abrahamowicz M, Li Y, Danoff D, Clarke AE. Routine immunologic tests in systemic lupus erythematosus: is there a need for more studies? *J Rheumatol*. 1996;23(11):1891–1896.
96. Palazzo L, Lindblom J, Mohan C, Parodis I. Current Insights on Biomarkers in Lupus Nephritis: a Systematic Review of the Literature. *J Clin Med*. 2022;11(19):5759. doi:10.3390/jcm11195759
97. Rahman P, Gladman DD, Ibanez D, Urowitz MB. Significance of isolated hematuria and isolated pyuria in systemic lupus erythematosus. *Lupus*. 2001;10(6):418–423. doi:10.1191/096120301678646164
98. Ushakova NA, Brodskii ES, Kovalenko AA, Bastrakov AI, Kozlova AA, Pavlov DS. Characteristics of lipid fractions of larvae of the black soldier fly *Hermetia illucens*. *Article Dokl Biochem Biophys*. 2016;468(1):209–212. doi:10.1134/S1607672916030145
99. Smith EMD, Jorgensen AL, Beresford MW, Group UJS. Do classic blood biomarkers of JSLE identify active lupus nephritis? Evidence from the UK JSLE Cohort Study. *Lupus*. 2017;26(11):1212–1217. doi:10.1177/0961203317702253
100. Suzuki M, Wiers KM, Klein-Gitelman MS, et al. Neutrophil gelatinase-associated lipocalin as a biomarker of disease activity in pediatric lupus nephritis. *Pediatr Nephrol*. 2008;23(3):403–412. doi:10.1007/s00467-007-0685-x
101. Mina R, von Scheven E, Ardoin SP, et al. Consensus treatment plans for induction therapy of newly diagnosed proliferative lupus nephritis in juvenile systemic lupus erythematosus. *Arthritis Care Res*. 2012;64(3):375–383. doi:10.1002/acr.21558
102. Brunner HI, Bennett MR, Abulaban K, et al. Development of a Novel Renal Activity Index of Lupus Nephritis in Children and Young Adults. *Arthritis Care Res*. 2016;68(7):1003–1011. doi:10.1002/acr.22762
103. Gulati G, Bennett MR, Abulaban K, et al. Prospective validation of a novel renal activity index of lupus nephritis. *Lupus*. 2017;26(9):927–936. doi:10.1177/0961203316684212

104. Cody EM, Wenderfer SE, Sullivan KE, et al. Urine biomarker score captures response to induction therapy with lupus nephritis. *Pediatr Nephrol.* 2023;38(8):2679–2688. doi:10.1007/s00467-023-05888-z
105. Brunner HI, Gulati G, Klein-Gitelman MS, et al. Urine biomarkers of chronic kidney damage and renal functional decline in childhood-onset systemic lupus erythematosus. *Pediatr Nephrol.* 2019;34(1):117–128. doi:10.1007/s00467-018-4049-5
106. Hanaoka H, Kiyokawa T, Iida H, et al. Comparison of renal response to four different induction therapies in Japanese patients with lupus nephritis class III or IV: a single-centre retrospective study. *PLoS One.* 2017;12(4):e0175152. doi:10.1371/journal.pone.0175152
107. Dimelow R, Liefgaard L, Green Y, Tomlinson R. Extrapolation of the Efficacy and Pharmacokinetics of Belimumab to Support its Use in Children with Lupus Nephritis. *Clin Pharmacokinet.* 2024;63(9):1313–1326. doi:10.1007/s40262-024-01422-y
108. Ginzler EM, Dooley MA, Aranow C, et al. Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. *N Engl J Med.* 2005;353(21):2219–2228. doi:10.1056/NEJMoa043731
109. Houssiau FA, Vasconcelos C, D’Cruz D, et al. Immunosuppressive therapy in lupus nephritis: the Euro-Lupus Nephritis Trial, a randomized trial of low-dose versus high-dose intravenous cyclophosphamide. *Arthritis Rheum.* 2002;46(8):2121–2131. doi:10.1002/art.10461
110. Balevic SJ, Randell R, Weiner D, et al. Pharmacokinetics of hydroxychloroquine in paediatric lupus: data from a novel, direct-to-family clinical trial. *Lupus Sci Med.* 2022;9(1):e000811. doi:10.1136/lupus-2022-000811
111. Zahr N, Urien S, Funck-Brentano C, et al. Evaluation of Hydroxychloroquine Blood Concentrations and Effects in Childhood-Onset Systemic Lupus Erythematosus. *Pharmaceuticals.* 2021;14(3):273. doi:10.3390/ph14030273
112. Silva PUJ, Oliveira MB, Vieira W, et al. Oral pigmentation as an adverse effect of chloroquine and hydroxychloroquine use: a scoping review. *Medicine.* 2022;101(11):e29044. doi:10.1097/MD.00000000000029044
113. Peng JP, Yang XY, Luo F, et al. Hydroxychloroquine-induced hyperpigmentation of the skin and bull’s-eye maculopathy in rheumatic patients: a case report and literature review. *Front Immunol.* 2024;15:1383343. doi:10.3389/fimmu.2024.1383343
114. Suhlrie A, Hennies I, Gellermann J, et al. Twelve-month outcome in juvenile proliferative lupus nephritis: results of the German registry study. *Pediatr Nephrol.* 2020;35(7):1235–1246. doi:10.1007/s00467-020-04501-x
115. Tanaka H, Watanabe S, Aizawa-Yashiro T, et al. Long-term tacrolimus-based immunosuppressive treatment for young patients with lupus nephritis: a prospective study in daily clinical practice. *Nephron Clin Pract.* 2013;121(3–4):c165–c173. doi:10.1159/000346149
116. Tanaka H, Aizawa T, Endo M. Long-term outcome of tacrolimus-based immunosuppressive treatment for patients with paediatric-onset lupus nephritis. *Nephrology.* 2024;29(12):901–908. doi:10.1111/nep.14406
117. Anders HJ, Furie R, Malvar A, et al. Effect of belimumab on kidney-related outcomes in patients with lupus nephritis: post hoc subgroup analyses of the Phase 3 BLISS-LN trial. *Nephrol Dial Transplant.* 2023;38(12):2733–2742. doi:10.1093/ndt/gfad167
118. Brunner HI, Abud-Mendoza C, Viola DO, et al. Safety and efficacy of intravenous belimumab in children with systemic lupus erythematosus: results from a randomised, placebo-controlled trial. *Ann Rheum Dis.* 2020;79(10):1340–1348. doi:10.1136/annrheumdis-2020-217101
119. Li H, Chen C, Yang H, Tu J. Efficacy and safety of belimumab combined with the standard regimen in treating children with lupus nephritis. *Eur J Pediatr.* 2024;183(9):3987–3995. doi:10.1007/s00431-024-05662-9
120. Aragon E, Resontoc LP, Chan YH, et al. Long-term outcomes with multi-targeted immunosuppressive protocol in children with severe proliferative lupus nephritis. *Lupus.* 2016;25(4):399–406. doi:10.1177/0961203315615220
121. Aragon E, Chan YH, Ng KH, Lau YW, Tan PH, Yap HK. Good outcomes with mycophenolate-cyclosporine-based induction protocol in children with severe proliferative lupus nephritis. *Lupus.* 2010;19(8):965–973. doi:10.1177/0961203310366855
122. Levy RA, Gonzalez-Rivera T, Khamashta M, et al. 10 Years of belimumab experience: what have we learnt? *Lupus.* 2021;30(11):1705–1721. doi:10.1177/09612033211028653
123. Rovin BH, Furie R, Latinis K, et al. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study. *Arthritis Rheum.* 2012;64(4):1215–1226. doi:10.1002/art.34359
124. Elshaer R, Jaber S, Odeh N, Arbili L, Al-Mayouf SM. Safety and efficacy of biologics in childhood systemic lupus erythematosus: a critical systematic review. *Clin Rheumatol.* 2024;43(3):863–877. doi:10.1007/s10067-023-06833-z
125. Tambralli A, Beukelman T, Cron RQ, Stoll ML. Safety and efficacy of rituximab in childhood-onset systemic lupus erythematosus and other rheumatic diseases. *J Rheumatol.* 2015;42(3):541–546. doi:10.3899/jrheum.140863
126. Lehman TJ, Singh C, Ramanathan A, et al. Prolonged improvement of childhood onset systemic lupus erythematosus following systematic administration of rituximab and cyclophosphamide. *Pediatr Rheumatol Online J.* 2014;12(1):3. doi:10.1186/1546-0096-12-3
127. Podolskaya A, Stadermann M, Pilkington C, Marks SD, Tullus K. B cell depletion therapy for 19 patients with refractory systemic lupus erythematosus. *Arch Dis Child.* 2008;93(5):401–406. doi:10.1136/adc.2007.126276
128. Sawhney S, Agarwal M. Rituximab use in pediatric systemic lupus erythematosus: indications, efficacy and safety in an Indian cohort. *Lupus.* 2021;30(11):1829–1836. doi:10.1177/09612033211034567
129. Hogan J, Godron A, Baudouin V, et al. Combination therapy of rituximab and mycophenolate mofetil in childhood lupus nephritis. *Pediatr Nephrol.* 2018;33(1):111–116. doi:10.1007/s00467-017-3767-4
130. Willems M, Haddad E, Niaudet P, et al. Rituximab therapy for childhood-onset systemic lupus erythematosus. *J Pediatr.* 2006;148(5):623–627. doi:10.1016/j.jpeds.2006.01.041
131. Zhang L, Cui JY, Zhang L. Clinical efficacy and safety of sirolimus in childhood-onset systemic lupus erythematosus in real world. *Medicine.* 2022;101(46):e31551. doi:10.1097/MD.00000000000031551
132. Cao H, Rao Y, Liu L, et al. The Efficacy and Safety of Leflunomide for the Treatment of Lupus Nephritis in Chinese Patients: systematic Review and Meta-Analysis. *PLoS One.* 2015;10(12):e0144548. doi:10.1371/journal.pone.0144548
133. Guiducci C, Gong M, Xu Z, et al. TLR recognition of self nucleic acids hampers glucocorticoid activity in lupus. *Nature.* 2010;465(7300):937–941. doi:10.1038/nature09102
134. Hanif M, Sarker C, Al-Abadi E, et al. Contributors to Organ Damage in Childhood Lupus: corticosteroid Use and Disease Activity. *Rheumatology.* 2024;keae592. doi:10.1093/rheumatology/keae592
135. Zhang E, Capponi S, Scobell R, et al. Real-world application of the pediatric Glucocorticoid Toxicity Index in childhood-onset lupus. In: *Seminars in Arthritis and Rheumatism.* Vol. 68. Elsevier; 2024:152516.
136. He X, Hu B, Zhang Y, et al. Treatment of two pediatric patients with refractory systemic lupus erythematosus using CD19-targeted CAR T-cells. *Autoimmun Rev.* 2024;24(1):103692. doi:10.1016/j.autrev.2024.103692

137. Wenderfer SE, Ruth NM, Brunner HI. Advances in the care of children with lupus nephritis. *Pediatr Res.* 2017;81(3):406–414. doi:10.1038/pr.2016.247
138. Wenderfer SE, Orjuela A, Dionne J. How common is chronic kidney disease in children with lupus nephritis? *Pediatr Nephrol.* 2023;38(6):1701–1705. doi:10.1007/s00467-022-05848-z

### International Journal of Nephrology and Renovascular Disease

### Publish your work in this journal

The International Journal of Nephrology and Renovascular Disease is an international, peer-reviewed open-access journal focusing on the pathophysiology of the kidney and vascular supply. Epidemiology, screening, diagnosis, and treatment interventions are covered as well as basic science, biochemical and immunological studies. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/international-journal-of-nephrology-and-renovascular-disease-journal>

**Dovepress**  
Taylor & Francis Group